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THE MODERN ASPECTS OF THE DIABETIC PROBLEM*

The Ludwig Kast Lecture†

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IT is a privilege and an honor to participate in your Postgraduate Week and especially to join with you in honoring Dr. Ludwig Kast, for whom this lecture was named and from whose proposal this great educational enterprise of yours has developed.

Basic concepts and fundamentals in the treatment of diabetes remain relatively constant. Only minute fragments of the enormous amount of investigation in this field become integrated into the permanent fabric of our understanding and into the clinical management of this disorder. The scanning of the accomplishments of investigators and the selection of the fruits of their endeavors that hold promise in clinical application are not always as simple as their formal appearance, reduced to a few sentences in a standard text, might infer.

I shall avail myself of the latitude permitted in the title of this

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† In honor of Dr. Ludwig Kast who first suggested the Graduate Fortnight.

paper by dealing with what I consider to be some of the problems which are in varying stages of solution.

Classification

It takes courage to come to grips with the problem of classifying diabetes. However, as components of the puzzle have fallen into place, a reasonable classification has evolved. Grades of severity of diabetes may alter as the variety of influences to which these patients are subject assert themselves. The diabetes may recede so far into the background that it is not detectable in some obese patients who reduce adequately their total caloric intake; others may be neglectful and experience unfavorable progression of the disorder. The diabetes in one patient may be classified differently at different times, for example, the obese patient who because of neglect, or ignorance, may lose weight because of the degree of glycosuria. When he becomes underweight under these influences he has increased his sensitivity to insulin; he is more prone to ketosis than he formerly was and his diabetes is much less stable than it had been. This transition from one phase of the disorder into another does not alter the practicability of the classification (Table I) if it is used in the light of good clinical judgment.

Primary or essential diabetes, because of its great frequency, our inability, not knowing its cause, to do more than reduce predisposing influences, and its proclivity for causing progressive degenerative disorders, presents a major clinical problem.

It is significant that ketosis, progressive degenerative changes and an apparent hereditary influence, as occur characteristically in primary diabetes, are not features of secondary diabetes. Furthermore, secondary diabetes is curable if the cause is identified and if it is practicable to remove it, for example, removal of a corticoid tumor.

The Enigma of the Prediabetic State

Probably all who have cared for many diabetic patients have had occasion to observe some of the characteristics of diabetes in individuals who lacked any detectable evidences of disturbed carbohydrate metabolism. Even the response to the glucose tolerance test has been normal. But, after some years have elapsed hyperglycemia and glycosuria appear. A common indication of a prediabetic state

TABLE I—A CLINICAL CLASSIFICATION OF DIABETES MELLITUS

I. Primary, or essential, diabetes—adult type
   A. *Relatively stable*
      Onset in adult life
      Overweight is usual (80% +)
      Relatively insensitive to insulin
      Not prone to develop ketosis, in the absence of acute complications
   B. *Unstable*—juvenile type
      Onset usually in childhood or youth
      Very sensitive to insulin
      Very susceptible to ketosis

II. Secondary diabetes
   A. Hyperadrenalism
      1. Cortical—Cushing's syndrome and primary aldosteronism
         —corticoid therapy
      2. Medullary—pheochromocytoma
   B. Hyperpituitarism
      1. Acromegaly
      2. Pituitary basophilism
      3. Therapy—adrenicotrophic (ACTH) and growth hormones
   C. Hyperthyroidism (rarely, if ever, a cause of clinical diabetes)
      1. Thyrotoxicosis
      2. Thyroid therapy
   D. Destruction or excision of islet tissue
      1. Hemochromatosis
      2. Pancreatitis
      3. Cystic disease or neoplasm of pancreas
      4. Removal of pancreas
      5. Trauma to pancreas (?)

is seen in women who give birth to large babies. The prediction that *the mother of an infant weighing more than 10 pounds* at birth will ultimately develop clinical diabetes is more likely than not to be fulfilled. This result is especially likely if the mother has diabetic relatives.

The *glucose tolerance test* as ordinarily employed is of value in detecting pre-clinical diabetes *in pregnant subjects* between the end of the fourth month and the termination of the pregnancy. The hyperglycemic response subsides after delivery. Hoet[1] attributes this abnormality, most frequent in patients with a family history of diabetes, to hypercorticism and its effect upon the islands of Langerhans.

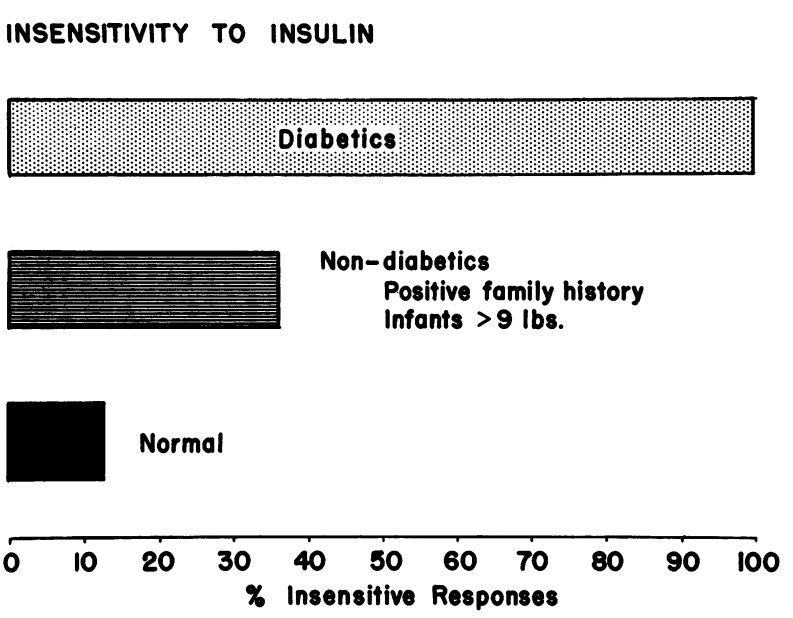

Fig. 1. Glucagon-free insulin sensitivity tests indicate that all adult diabetics' tests showed relative insensitivity to insulin. Thirty-eight per cent of non-diabetic women who had a family history of diabetes and who had given birth to infants weighing more than 9 pounds were relatively insensitive to insulin in contrast to 12.5 per cent of presumably normal men and women.

Fig. 2. Results of steroid-glucose tolerance tests (Somogyi-Nelson). A family history of diabetes reflects unfavorably in this test when either prednisone or prednisolone was given prior to the ingestion of the glucose. Reprinted by permission of K. M. West and American Diabetes Association, ref. 5.

Furthermore, he believes that correction of this disturbance in carbohydrate metabolism, by giving insulin, will reduce fetal mortality. Time will tell whether or not the appearance of diabetes in the mother later in life will in this manner also be prevented.

Detection of a *relative insensitivity to insulin* may indicate a prediabetic state. This has been suggested by Anderson's observations[2] and by a survey made by Drs. K. Young, C. F. Lee and G. Schless[3] at the Pennsylvania Hospital. Women who had less than a 10 per cent reduction in the blood sugar level within ten minutes after the intravenous administration of 3 units of glucagon-free crystalline insulin are considered to be relatively insensitive to insulin. All adult diabetics were found, by this modified Anderson[2] test,* to be relatively insensitive to insulin, as were 36 per cent of nondiabetic women who had a family history of diabetes and who had borne infants weighing more than 9 pounds. Of the women, 29 in number, who had babies weighing more than 9 pounds but who had no family history of diabetes, 38 per cent were unusually insensitive to insulin. In contrast, only 12.5 per cent of presumably entirely normal women and men showed relative insensitivity to insulin (Fig. 1).

Functional burdens on the pancreatic islets may expose reduced reserve capacity to deal with carbohydrate long before clinical diabetes is manifest. In the adult, a blood sugar value in excess of 130 mg. per cent (Folin-Wu) two hours *after the ingestion of 100 gm. of glucose* in the fasting state is presumptive evidence of an early diabetes. This is an effective screening test for relatives of diabetics. However, this test may reveal no abnormality. Functional stress may be further magnified, as suggested by Fajans and Conn[4] and by West.[5] The *glucose tolerance test is modified by giving a steroid* eight and one half hours before the oral administration of glucose. Prednisone or prednisolone exerts greater hyperglycemic effects than cortisone acetate or hydrocortisone.[5] The true glucose values obtained by the Somogyi-Nelson method were determined two hours after the ingestion of glucose. The interpretation that abnormally high blood sugar values indicate a prediabetic state may be considered speculative but the significant increase in the incidence of high values in relatives of diabetics as compared with those who had no diabetic relatives is supporting evidence. The results reported by West[5] are shown in

* This test involves giving 3 units of glucagon-free crystalline insulin intravenously to a patient in the fasting state and taking blood samples at two minute intervals for ten minutes.

Figure 2. These support the studies of Fajans and Conn[4] which indicated that 24 per cent of the subjects with a positive family history showed substantially abnormal glucose tolerance curves after receiving cortisone. Only 3 per cent of subjects having no family history of diabetes showed similar impairment as indicated by the cortisone-glucose tolerance tests.

Other, but uncommon, stigmata of the prediabetic state are *retinal changes* and *neuropathies*, both being indistinguishable from those seen in fully developed diabetes. *Mild degrees of hypoglycemia* have been reported as being an early clinical indication of diabetes.[6] These criteria of pre and early diabetes are more likely to be missed than is the case of the mother of an 11 pound baby.

Obesity affecting members of diabetic families is so common and so frequently a forerunner of diabetes that one is justified in considering it as inseparable from the unknown processes which prevail in the prediabetic state in adults. Unlike the prediabetic retinal and neuropathic changes, obesity is also a precipitating factor. The ease with which diabetes is controlled by the therapeutic reduction in weight of the obese diabetic is presumptive evidence that the prevention or correction of obesity in members of diabetic families may prevent the development of clinical diabetes.

Until the enigma of the prediabetic is solved, the foregoing means of its detection serve as indications for measures aimed to prevent clinical diabetes. The measures at hand that may serve this purpose, as well as control mild forms of diabetes, are: the avoidance of overeating, the correction of obesity, and control with diet and insulin of the disturbance in carbohydrate metabolism during pregnancy and during other episodes which may be accompanied by what appears to be a transitory diabetes, for example, carbuncles. These measures and a suitable regimen of daily exercise offer some prospects for the prevention of diabetes.

The Overweight Diabetic

Approximately 82 per cent of adult diabetics are overweight when they seek treatment. Too little effort is made to reduce the weights of these patients and resort to insulin or tolbutamide is adopted too readily. This is the easy way, but it permits the patient to remain overweight in most instances. A study of the composite experience of

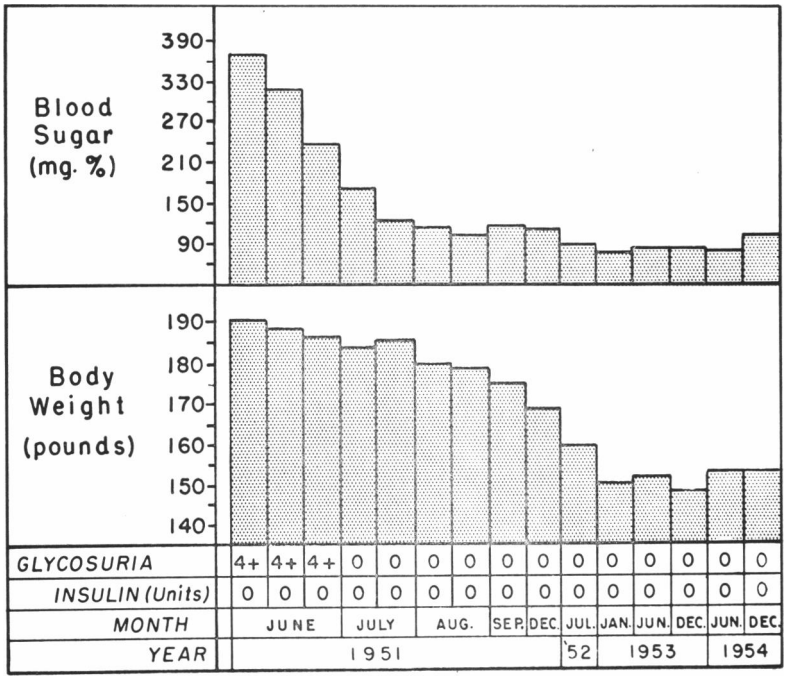

Fig. 3. Typical effect of therapeutic undernutrition in obese diabetics. The clearing of glycosuria and the correction of the hyperglycemia are associated with the reduced diet and the decrease in body weight.

insurance companies of the effect of overweight on longevity, and especially as it applies to diabetic patients, is enlightening. Overweight diabetics have a mortality rate 2.5 times that of normal, but if the degree of overweight exceeds 25 per cent, the mortality is eight times that normally expected.

The effective reduction of the obese diabetic involves a well-planned campaign that may of necessity be lifelong. The obese diabetic should not intensify his or her appetite by excessive physical exercise or by insulin therapy. Fortunately, tolbutamide does not increase the appetite. However, if it is employed in the treatment of the obese diabetic, diet therapy will be given little credit and less heed by all but the exceptional patient.

Reduction of the caloric intake, invoking the principles established some forty years ago by Dr. Frederick M. Allen, remains the treatment of choice for these patients. If prescribed and if adhered to, the weight reduction diet will suffice without drug therapy in the majority

of adult diabetics. The degree of success will reflect the zeal and confidence with which the treatment is instituted. The control of glycosuria and hyperglycemia by undernutrition is illustrated in Figure 3. The weight reduction regimen supplemented with appropriate amounts of vitamins is a temporary measure, following which additions to the diet adequate to maintain a satisfactory state of nutrition are made. My diabetics' diets closely approach that of normal individuals after undernutrition is no longer needed. Severe restrictions are unnecessary, but the respective meals from day to day must be uniform if good control of the diabetes is to be maintained. The evidence that good control should be achieved and maintained is overwhelming. All will agree that during acute complications, insulin should be given to overweight diabetics to counteract the tendencies to ketosis at such times.

Selection of Drug Therapy

Dietary considerations are necessary for all diabetic patients. *Tolbutamide therapy* is probably next in order of frequency in the treatment for new cases of uncomplicated diabetes. It is a treatment of convenience not requiring injections. All diabetic patients who developed diabetes after 40 years of age, who are not appreciably overweight, who have no acute complications, and who would formerly have *required insulin to control the diabetes* are proper candidates for trial therapy with tolbutamide. For those who are overweight, tolbutamide therapy may be given advantageously, but this should be considered a temporary measure and one to be discontinued when a suitable reduction in weight achieves control of the diabetes without it. Substitution of tolbutamide therapy for correction of obesity will probably be widespread. This practice is to be deprecated.

In more than two-thirds of the patients referred to, the diabetes will respond adequately to tolbutamide, which is ineffective when the diabetes has developed in youth. Also, it is ineffective in the presence of acute febrile complications and with rare exceptions in patients who develop ketonuria readily, hence the need for adequate training in insulin therapy as, sooner or later, the diabetic, as is the case in the nondiabetic will have acute complications to contend with.

In considering *tolbutamide* (Orinase) *therapy*, patients who have developed diabetes in childhood or youth may be excluded. For the

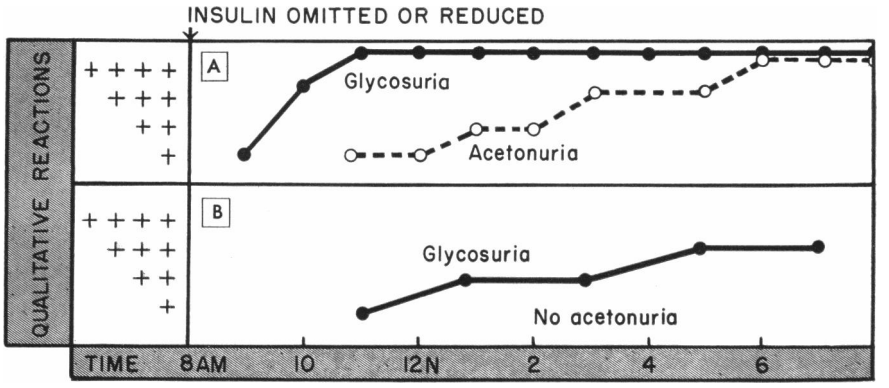

Fig. 4. Predicting the effects of tolbutamide. Patient A: Increasing glycosuria and acetonuria following the omission or appreciable reduction of insulin indicate that, in all likelihood, tolbutamide will not be effective. Patient B: Glycosuria but no acetonuria is presumptive evidence that tolbutamide therapy will be effective.

"adult acquired diabetes" it is a good plan to be sure that the patient needs drug therapy before embarking on a treatment that may not be necessary. Even specialists in the treatment of diabetes have been surprised to find that in many of their patients past middle age no glycosuria nor hyperglycemia followed the withdrawal of insulin. But in those cases in which insulin is actually needed, it may be abruptly withdrawn when the requirement does not exceed 20 units daily. If glycosuria occurs in increasing amounts, a trial of tolbutamide therapy is justified. Prompt control of the glycosuria will be proof of its effectiveness. If the insulin dosage exceeds 20 units, the amount given may be reduced by one-half for the first and omitted on the second day if no glycosuria occurs.

The prompt appearance of ketonuria, and in increasing amounts, during the first twelve hours indicates that no benefit need to be expected from tolbutamide and that insulin therapy should be promptly resumed if unfavorable progression of the ketosis is to be avoided. An instance of these findings is depicted in Figure 4 (Patient A).

On the other hand, if no ketonuria appears when insulin is discontinued, as in the case of Patient B (Fig. 4), it is highly probable that tolbutamide therapy will be adequate to control the diabetes.

Hypoglycemia, in our experience, is an uncommon complication of this therapy. Possibly this is because we do not give more than 1.5 gm. daily and more often less than this amount.

Apparent side effects are few, occurring in less than 3 per cent of cases. Skin rashes—urticarial, macular, eruptions or flushing—with pruritus are most common. If of mild degree, they tend to subside without interrupting the therapy. Leukopenia, disturbed bromsulfalein tests and elevated alkaline serum phosphatase values in mild and transitory forms have been observed but are quite rare.

If tolbutamide is given only to patients who would otherwise be obliged to take insulin, approximately 33 per cent must, in my experience, resume insulin within four to ten months without any apparent cause. This experience would be largely obscured if one yields to the temptation to prescribe tolbutamide for patients whose diabetes could be controlled by diet therapy alone.

Though many thousands of patients have taken tolbutamide for many months without apparent harm, it would be well to consider it as still on trial until time has shown it to maintain its effectiveness without untoward effects indefinitely.

Insulin is the ideal physiological agent. Because of the inconvenience of its administration, however, its use will probably be increasingly restricted to those patients whose diabetes cannot be controlled by diet alone, or with, oral therapy.

Insulin therapy is imperative in all juvenile diabetics and in all adults who acquired diabetes in youth and in those who develop ketonuria abruptly and in increasing amounts following the omission, or an appreciable reduction, of insulin.

Insulin is essential in the treatment of diabetes during acute infections, ketosis and surgery, and it is equally essential for the pregnant diabetic.

The selection of the appropriate insulin therapy is complicated by the fact that there are six insulins commercially available in this country, and if one writes for an international audience the number is increased to eight by including the rapidly acting amorphous insulin zinc suspension (semi-lente) and a long acting crystalline insulin zinc suspension (ultra-lente). There are three *rapidly acting insulins*—regular, crystalline and semi-lente; three *intermediate acting insulins*—globin, isophane (NPH) and lente; and two *long acting insulins*—protamine zinc and ultra-lente.

Some diabetics do well with a single dose of an intermediate acting *insulin* (globin, isophane [NPH] or lente) one hour before breakfast.

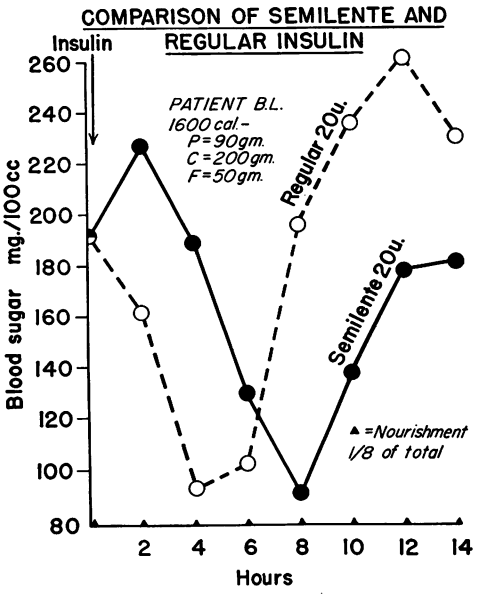

Fig. 5. The speed of action, the degree and duration of effect of semi-lente insulin compared with those of regular insulin. Identical amounts of nourishment were given in liquid form at two-hour intervals.

Others require the addition of crystalline insulin—rapidly acting—to an intermediate insulin—in my experience NPH is preferable. For the control of unstable diabetes, this mixture given one half hour before breakfast and a small amount of NPH insulin after supper or at bedtime has served us best. The total amount needed may be tried as a 2:1 mixture of crystalline and protamine zinc insulins given before breakfast. The efficiency of this plan of therapy is occasionally so good it is worth a trial. Mixtures of semi-lente and ultra-lente insulins, titrated to the needs of the individual, promise to increase considerably the number of patients who will achieve good control by one daily injection.

It was hoped that the "lente family of insulins" would cover the needs of all diabetics requiring insulin. That this is not the case is indicated in Figure 5. Regular insulin is shown to reduce the blood sugar more rapidly than the rapidly acting amorphous insulin zinc suspension (semi-lente) insulin, hence is the insulin of choice when greatest possible speed of action is desired. The method of comparing the effects of these two insulins, as shown in Figure 5, has proven to be most effective.

The day's diet is prepared in liquid form, and equal fractions of the total are given at two-hour intervals. The metabolic burden of these closely placed nourishments sharpens appreciably the appraisal of the contrast of speed, degree and duration of effect.

During acute, but minor, complications additions to the usual doses of insulin may suffice, or crystalline insulin may be given at four hour intervals without disturbing the usual program. For severe complications we have found no plan so effective as crystalline insulin given every six hours with the diet equally divided into four nourishments and given also at six hour intervals.[7, 8]

Some of the perplexing problems concerning diabetes have been touched on. Many could not be included. Attention has been directed to the prediabetic state, its detection, and the potential advantages its recognition may offer. An attempt has been made to place diet, tolbutamide and insulin therapies in their appropriate and respective places, and a comprehensive plan of insulin therapy, that lends itself to the substitution of the insulin of one's choice, has been submitted.

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